November 5, 2014

Comments submitted to the SAB CAAC via email to Thomas Carpenter

Public statement from Nancy Beck, PhD, DABT, on behalf of the American Chemistry Council, to the Scientific Advisory Board Chemical Assessment Advisory Committee (CAAC) for the review of the Draft IRIS Trimethylbenzene (TMB) Assessment.

Good Afternoon.

I am providing remarks today on behalf of the American Chemistry Council (ACC). We have read your draft report and want to thank you all again for the time and energy you are putting into this review. It is clear that each of you are taking your responsibilities seriously and we recognize that volunteering to be on this review panel is likely more of a time commitment than you expected. Not only is it important to get the TMB science correct, but as this is one of the first semi-revised IRIS assessments you are reviewing, your comments on the structure, approach and methodologies used in this assessment will have precedent setting implications for many other IRIS assessments.

There are many recommendations in the draft report that ACC supports and due to the time constraints I will not point them out. Thus my comments today will focus on potential areas where public input may help to improve the clarity of your recommendations.

1) **Consensus is important**. We recognize that reaching consensus is not easy. Unfortunately, there appear to be multiple areas where the panel is divided (e.g., considering C-9 data, applying uncertainty factors, addressing reversibility, evaluating EPA's responses to public comments). ACC encourages the panel to strive to reach consensus as many of these topics are critically important to the assessment and a consensus review would be helpful. Consideration of the EPA Office of Pesticide Programs final rule exempting C-9 Rich Aromatic Hydrocarbons from tolerance requirements may be very helpful to you. This information has been provided.

2) **The most useful recommendations are those that go beyond suggesting 'further discussion'**. There are a few places in the report (e.g., the discussion of consideration of the C-9 fraction) where you recommend further or more robust discussion of a topic. In our experience, these types of recommendations are not as useful as ones that include a suggestion to also re-evaluate the determinations made in light of a more robust characterization of the topic of concern. Without such a recommendation, we have seen that EPA staff often expand descriptions but don't necessarily re-evaluate determinations in light of those descriptions. While we think this is implicit in your recommendation, it would be helpful to clearly state this.

3) **Reliance on a reversible endpoint for the RfC/RfD may not be appropriate for all situations.** Historically, the IRIS program has not relied on reversible effects when setting IRIS values. While a chronic RfC is derived to represent a lifetime of exposure, in many situations, when used by state risk assessors and others, the duration is adjusted from 70 years to represent actual exposures (e.g. a 10 year, 25 year or 35 year exposure would all be considered chronic). As these time frames are frequently adjusted based on site specific information, the issue of reversibility would then become very relevant as there is indeed a post exposure period. If the IRIS value were based on a reversible endpoint, this value would need to be caveated noting that it may not be relevant for exposures that are less-than-lifetime as no adverse effect may be seen once the exposure is stopped. Derivations of values based on shorter term exposures would have to fully consider the aspect of reversibility when interpreting the data. The panel may want to consider this when making their recommendations for the appropriate study and point of departure. Multiple approaches may be appropriate. While the IRIS glossary does not speak to reversibility, relying on reversible effects has not been the norm for the IRIS program and should not be considered lightly. Thus we ask the panel to consider these issues and also try to clarify their interpretation of the pain sensitivity endpoint and how it should and should not be used.

4) **Derivation of sub-chronic values should not be considered lightly**. While we are not necessarily opposed to the derivation of sub-chronic values by the IRIS program, we note that the IRIS program has been struggling for many years to develop their expertise to make the program the gold-standard for chronic non-cancer values and cancer values and to develop these assessments in a timely manner. This has not proven to be an easy task, as has been noted in multiple NAS reports. Many assessments take more than seven years to complete. While it may seem easy and logical to include sub-chronic derivations, our concern is that adding these values to IRIS assessments will slow down the process tremendously. In addition for this assessment, there should be an opportunity for public comment on a draft approach before EPA finalizes a newly derived value. Similarly, the issue of reversibility would become important and thus a discussion of what the correct points of departure are, in addition to a discussion of uncertainty factors, would also likely

slow down the completion of the chronic assessment. We also note that other federal agencies, like ATSDR, provide sub-chronic and acute hazard values for chemical assessments.

The draft cover letter notes that regulatory agencies are frequently required to address risks associated with short-term exposures. Perhaps one recommendation could be that the problem formulation conducted for IRIS assessments include consideration of the exposure durations of concern before beginning the assessment. This may help in planning the assessment, including collecting studies to consider, rather than trying to retrofit data to fit other exposure durations when the agency is at the final stages of the chronic assessment.

5) **Clarifying the Cover Letter and Executive Summary**. While the report covers many topics in depth, the cover letter and executive summary mention only a few of the reports' findings and, appropriately, the level of depth is much more limited. As not every topic area from the charge is addressed, it is unclear why certain topics were the focus of the cover letter and executive summary and others are not mentioned. It may be helpful to clarify which recommendations are most important to the CAAC. A thorough review of how the cover letter and executive summary relate to the full final report may be helpful.

6) **Comments on the preamble are very important**. We appreciate the time given to address the preamble of this and other IRIS assessments. We are already seeing other program offices refer to IRIS assessments as fully consistent with NAS recommendations and also consistent with systematic review approaches. As we know this is not the case, it is important that IRIS assessments, like the TMB assessment, are clear on this as well. Thus having a preamble that accurately describes approaches taken in the TMB assessment is important. Your draft report notes (at page 7) that the preamble provides a clear description of the process that is followed, however you further note that it is confusing as to what applies to the TMB assessment. As the panel members recognize the confusion in the preamble, it would be helpful to send a clear message to EPA regarding what should and should not be presented in the preamble. We would request that the panel make a clearer recommendation, particularly regarding your recommendations for sections 3-7 of the preamble.

7) **Clarification of comments on PBPK modeling would be helpful**. It was encouraging to see such a rigorous review of EPA's PBPK modeling and we applaud the panel for looking at these data in depth. At one point in the letter (see page 2) the panel notes the importance of EPA commissioning an independent peer review of the PBPK models used. While the report provides many details on the modeling, it is not clear if the panel is recommending a more extensive external independent review or if the panel's comments are acting as that peer review. Alternatively, the letter could be recommending that in the future PBPK models be

reviewed separate from the draft IRIS assessment. More clarity on your recommendations would be helpful.

8) **Clarifying comments on improving systematic review**. As you are aware, moving IRIS towards systematic reviews is one of Dr. Olden's goals. On page 13 of your draft report, you note that the "The process of systematic review still needs development." It is unclear whether this paragraph is suggesting that the overall approach generally needs development, or if the TMB assessment needs to be further developed in this regard. Clarification of this comment would be helpful.

Thank you again for the time and energy you have put into this important review. I would be happy to answer any questions.